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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| EXAMINER | |
|---|---|
| BARNHART, LORA ELIZABETH | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1651 | |

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| 10/20/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/730,549 | LAUGHLIN ET AL. | |
| | Examiner | Art Unit | |
| | Lora E. Barnhart | 1651 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4,5,9-12,21-43,48,50-54,56,57 and 62-69* is/are pending in the application.

4a) Of the above claim(s) *5,9,22,37-39 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,10-12,21,23-36,40-43,50-54,56,57 and 62-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendments*

Applicant's amendments filed 9/24/09 to claims 1, 54, and 57 have been entered. No claims have been canceled or added in this reply. Claims 1, 2, 4, 5, 9-12, 21-43, 48, 50-54, 56, 57, and 62-69 remain pending in the current application, of which claims 1, 2, 4, 10-12, 21, 23-36, 40-43, 50-54, 56, 57, and 62-69 are being considered on their merits. Claims 5, 9, 22, 37-39, and 48 remain withdrawn from consideration at this time. Prior art references not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Applicant should note that claims 50-53 are withdrawn because they depend from withdrawn claim 48. They are not "previously presented" as indicated in the most recent claim listing.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order

for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 10-12, 21, 23-36, 40-43, 50-54, 56, 57, and 62-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strauer et al. (2002, *Circulation* 106: 1913-1918) taken in view of Shake et al. (2002, *Annals of Thoracic Surgery* 73: 1919-1926), Ueno et al. (U.S. Patent Application Publication 2002/0037278), Kocher et al. (2001, *Nature Medicine* 7: 430-436), and Itescu (2003, U.S. Patent Application Publication 2003/0199464).

Strauer et al. teach isolating bone marrow (BM) from humans (page 1914, column 1, paragraph 5); isolating bone marrow mononuclear cells (BMCs) therefrom; cultivating them overnight in a buffered tissue culture medium comprising autologous serum (page 1914, column 2, paragraph 1), and administering over $10^6$ BM-MNCs to the ischemic tissue using a balloon catheter, specifically via intracoronary administration at ischemic myocardium in a subject in need thereof (page 1914, column 2, paragraph 2; page 1915, column 2, paragraph 3). Strauer et al. teach administering between $1.5x10^6$ and $4x10^6$ BM-MNCs 6 or 7 times, *i.e.*, between $9x10^6$ and $2.8x10^7$ BM-MNCs; Strauer et al. also teach that 0.65% of BM-MNCs are $AC133^+$ ($CD133^+$). Therefore, Strauer et al. teach administering between $5.9x10^4$ and $1.8x10^5$ $AC133^+$ EPCs. Strauer et al. teach that said injections resulted in improved cardiac function, cardiac geometry, and contractility (page 1915, column 2). Strauer et al. teach that their BMCs comprise mesenchymal stem cells (MSCs) as well as endothelial progenitor cells (EPCs; page 1916, column 2, paragraph 2).

Strauer et al. do not teach enriching $CD34^+CD133^+$ EPCs at least two-fold prior to administration to the subject. Strauer et al. do not teach coadministering mesenchymal stem cells (MSCs) that have been enriched at least two-fold prior to administration. Strauer et al. do not teach administering cells in the ratios recited in claims 28, 53, 67, and 68. Strauer et al. do not teach all of the modes of administration recited in claims 29-32. Strauer et al. do not teach coadministering the cells with VEGF or any recombinant polypeptide, as in claims 40-43. Strauer et al. do not teach administering allogeneic EPCs.

Shake et al. teach isolating MSCs from bone marrow and culturing them such that hematopoietic cells, fibroblasts, and non-MSC adherent cells are washed away, yielding a purified MSC culture (page 1919, column 2, through page 1920, column 1). Shake et al. teach administering said MSCs directly to an infarcted region of heart tissue in recipient pigs (page 1920, column 2). Shake et al. teach that MSCs so administered engraft into the host myocardium, express muscle-specific proteins, and have a beneficial impact on cardiac remodeling after myocardial infarction (page 1923, column 1).

Ueno et al. teach methods for treating ischemic tissues by administering bone marrow mononuclear cells; Ueno et al. teach that the administration may be local or systemic and may be carried out via injection or infusion into arteries or veins, directly into an occlusion, or application into a tissue or organ of interest (paragraphs 0034 and 0035). Ueno et al. teach that large amounts of cells may be administered to patients safely (paragraph 0037) and that the number of cells administered is optimizable

(paragraph 0034). Ueno et al. teach coadministering recombinant VEGF with the BMCs (paragraph 0042).

Kocher et al. teach that bone-marrow-derived angioblasts, which express AC133 (i.e., CD133) and CD34, among other markers (page 431, column 2, last sentence), promote revascularization of infarcted myocardium (Abstract; page 432, column 2, paragraph 2; Figure 3). Kocher et al. teach that angioblasts isolated to 98% purity express AC133 (page 435, column 1, paragraph 4). Kocher et al. teach that administration of their $CD34^+$ $AC133^+$ cells may be combined with other therapies (Abstract; page 435, column 1, paragraph 3).

Itescu teaches methods for regenerating myocardial tissue after ischemic damage by promoting neovascularization with an injection of endothelial progenitor cells (paragraph 0055). The EPCs of Itescu are found in bone marrow (paragraph 0056), express CD34 and CD133 (paragraph 0061), and may be allogeneic with respect to the recipient (paragraph 0057). Itescu teaches that the number of cells administered to the patient may vary (paragraph 0056), as may the location of the injection (paragraph 0061).

A person of ordinary skill in the art would have had a reasonable expectation of success in enriching the $CD34^+CD133^+$ EPCs within the BM-MNCs of Strauer et al. at least twofold because Kocher et al. teach methods for enriching such cells to 98% purity. The skilled artisan would have been motivated to enrich the $CD34^+CD133^+$ EPCs in the administered composition of Strauer et al. because Kocher et al. recognized that $CD133^+$ cells promote neovascularization of ischemic tissue; therefore, administering

more cells known at the time of the invention to achieve the desired result of Strauer et al. would improve the outcome of the method of Strauer et al.

The person of ordinary skill in the art would have had a further reasonable expectation of success in coadministering the EPCs of Strauer et al. with the purified MSCs of Shake et al. because the cited references teach that both cells promote healing after myocardial infarction. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted). See M.P.E.P. § 2144.06. Since Shake et al. teach that their MSCs are “purified” after their culturing step, the level of enrichment would have been a matter of routine optimization at the time of the invention, the skilled artisan recognizing that Shake et al. identified a property of MSCs (i.e., cardiac remodeling) and that it would have been desirable to administer as many cells with that property as possible in treating myocardial infarction.

The person of ordinary skill in the art would have had a further reasonable expectation of success in coadministering the VEGF of Ueno et al. with the cells of Strauer et al. and Shake et al. in the method of Strauer et al. because Ueno et al. teach methods for administering recombinant polypeptides and that such polypeptides may be coadministered with cells. The skilled artisan would have been motivated to include VEGF with the stem cells in the method of Strauer et al. in view of Shake et al. because

Ueno et al. teach that VEGF is a growth factor that promotes neovascularization upon administration to a patient.

The person of ordinary skill in the art would have had a further reasonable expectation of success in administering allogeneic cells in the method of Strauer et al. in view of Shake et al. because Itescu teaches that allogeneic EPCs promote neovascularization. The skilled artisan would have been motivated to administer allogeneic EPCs in the method of Strauer et al. in view of Shake et al. for the expected benefit that the pool of donor cells would be dramatically increased in size.

The selection of the mode of administration of the cells in the method of Strauer et al. in view of Shake et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Ueno et al. and Itescu both teach that ischemia may be treated bone marrow-derived cells administered in any of a variety of means. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the number of each type of cell to administer in the method of Strauer et al. in view of Shake et al. would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Strauer et al., Shake et al., Ueno et al., and Itescu all teach that these numbers may be modified depending on the desired outcome. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to enrich the $CD34^{+}CD133^{+}$ EPCs from the BM-MNCs of

Strauer et al. using the methods of Kocher et al. and administer more such $CD34^+CD133^+$ EPCs with the purified mesenchymal stem cells of Shake et al. in the method of Strauer et al. because Kocher et al. and Shake et al. teach that $CD34^+CD133^+$ EPCs and MSCs, respectively, promote neovascularization. It would have been further obvious to coadminister recombinant VEGF with the cells in the method of Strauer et al. in view of Shake et al. because Ueno et al. teach that VEGF is a growth factor that promotes neovascularization and aids in treating ischemia. It would have been further obvious to administer allogeneic EPCs in the method of Strauer et al. in view of Shake et al. because Itescu teaches that allogeneic EPCs promote neovascularization. Finally, it would have been further obvious to vary the numbers of each type of cell administered and the mode of administration because Strauer et al., Shake et al., Ueno et al., and Itescu concur that these are optimizable variables for the reasons discussed above.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Regarding this rejection, applicant alleges that Strauer does not teach that their cells are AC133+ and CD34+. Reply, page 14, last paragraph. Applicant alleges that Strauer did not recognize that their cells are endothelial progenitor cells. Reply, page 14, last paragraph continued to page 15. Applicant alleges that Kocher does not teach purifying CD34+ AC133+ cells to 98% purity. Reply, page 15, second paragraph. These arguments have been fully considered, but they are not persuasive.

The claims do not require that the CD34+ CD133+ cells be purified to any particular degree. Kocher teaches that bone marrow contains CD34+ CD133+ cells, and applicant has stipulated to this point in the reply at page 15, last paragraph. The method **comprises** administering EPCs and MSCs, so additional cell types may be included in the administration step. See M.P.E.P. § 2111.03.

In response to applicant's argument that Strauer did not recognize that their CD34+ CD133+ cells are EPCs, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In this case, Strauer and Shake establish that CD34+ CD133+ cells and MSCs both regenerate damaged myocardium, so the motivation to combine the two types flows from those references.

***No claims are allowed. No claims are free of the art.***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651